Regional and Ethnic Influences on the Response to Empagliflozin in Patients with Heart Failure and a Preserved Ejection Fraction: Results from the EMPEROR-Preserved Trial

Vijay Chopra[1] on behalf of the EMPEROR-Preserved Committees and Investigators

[1]Max Super Speciality Hospital, New Delhi, India

EMPEROR Heart failure studies

BACKGROUND

- In the EMPEROR-Preserved trial, empagliflozin 10 mg given once daily in addition to standard of care therapy reduced the risk of the primary endpoint (time to first event of a composite of cardiovascular [CV] death or hospitalization for heart failure [HHF]) in patients with heart failure and a preserved ejection fraction (HFpEF), regardless of the presence or absence of diabetes.[1]

Scan QR code for an **interactive** electronic device-friendly copy of the poster
https://bit.ly/3oOdTDC

OBJECTIVE

- To explore the influence of region and race/ethnicity on the effects of empagliflozin versus placebo in EMPEROR-Preserved.

METHODS

- In the EMPEROR-Preserved trial, 5988 patients with left ventricular ejection fraction (LVEF) >40% were randomized to receive empagliflozin 10 mg once daily or placebo plus standard of care.
- The primary endpoint was time to first CV death or HHF. The components of the primary outcome were also analyzed, including CV death, time to first HHF, and total (first and recurrent) HHF.
- For time-to-first-event analyses, the effects of empagliflozin versus placebo by region and race/ethnicity were assessed using a Cox regression model.
- For total (first and recurrent) analyses, the effects of empagliflozin versus placebo by region and race/ethnicity were assessed using a joint frailty model.

RESULTS

- A majority of the EMPEROR-Preserved participants were from Europe (2968 [49.57%]), 1515 (25.30%) were from Latin America, 719 (12.01%) from North America and 786 (13.13%) from Asia (**Table 1**).
- Most participants were White (4542 [75.85%]; **Table 1**).

Table 1. Distribution of EMPEROR-Preserved participants by region and race/ethnicity

Race/ethnicity, n (%)	Overall (N=5988)	Region			
		North America n=719	Latin American n=1515	Europe* n=2968	Asia† n=786
White	4542 (75.85)	616 (85.67)	1081 (71.35)	2845 (95.86)	0
Black/African American	258 (4.31)	80 (11.13)	144 (9.50)	34 (1.15)	0
Asian	824 (13.76)	12 (1.67)	21 (1.39)	5 (0.17)	786 (100.00)
Other‡	362 (6.05)	9 (1.25)	269 (17.76)	84 (2.83)	0
Missing	2 (<0.1)	2 (0.28)	0	0	0

*South Africa (n=163) and Australia (n=116) are included in the 'Europe' category.
†India (n=100) is included in the 'Asia' category.
‡'Other' includes any participant who selected more than 1 race category.

- Some differences in baseline characteristics by region were observed. Participants from Europe and North America were generally older, had higher body mass index (BMI), were more likely to have New York Heart Association (NYHA) functional class III–IV, had lower estimated glomerular filtration rate, were more likely to have atrial fibrillation, and were more likely to be receiving loop or high-ceiling diuretics compared with participants from Latin America or Asia (**Table 2**).

Table 2. Baseline characteristics by region

Characteristics	North America n=719	Latin America n=1515	Europe* n=2968	Asia† n=786
Age, years, mean ± SD	72.71±10.28	69.45±10.19	73.14±8.34	71.13±9.94
Female, n (%)	316 (43.95)	716 (47.26)	1360 (45.82)	284 (36.13)
Body mass index, kg/m², mean ± SD	32.23±6.39	29.75±5.66	30.56±5.54	25.08±4.19
Systolic blood pressure, mmHg, mean ± SD	130.69±17.10	130.34±15.81	133.49±15.01	129.56±15.59
NYHA class III–IV, n (%)	175 (24.34)	231 (15.25)	609 (20.52)	86 (10.94)
Duration of heart failure, years, median (IQR)	2.94 (1.08, 6.34)	2.63 (1.06, 5.92)	2.64 (0.99, 5.73)	2.22 (0.80, 5.69)
NT-proBNP, pg/ml, median (IQR)	1043.00 (528.00, 1860.00)	835.00 (449.00, 1637.00)	978.00 (492.00, 1665.00)	1155.00 (606.00, 2021.00)
eGFR, ml/min/1.73 m², mean ± SD	56.28±21.37	62.06±19.83	59.98±18.77	64.33±19.77
Medical history, n (%)				
Atrial fibrillation	405 (56.33)	440 (29.04)	1794 (60.44)	418 (53.18)
Hypertension	681 (94.71)	1378 (90.96)	2732 (92.05)	633 (80.53)
Diabetes	365 (50.76)	814 (53.73)	1396 (47.04)	363 (46.18)
Treatment for heart failure, n (%)				
All diuretics	620 (86.23)	1287 (84.95)	2649 (89.25)	607 (77.23)
Loop diuretics or high-ceiling diuretics	547 (76.08)	853 (56.30)	2155 (72.61)	499 (63.49)
ACEi or ARB (excluding ARNi)	467 (64.95)	1283 (84.69)	2442 (82.28)	513 (65.27)
ACEi, ARB or ARNi	498 (69.26)	1323 (87.33)	2472 (83.29)	539 (68.58)
Beta-blocker	614 (85.40)	1311 (86.53)	2622 (88.34)	620 (78.88)
Mineralocorticoid receptor antagonist	169 (23.50)	603 (39.80)	1133 (38.17)	339 (43.13)

*South Africa (n=163) and Australia (n=116) are included in the 'Europe' category.
†India (n=100) is included in the 'Asia' category.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

- With regards to baseline characteristics by race/ethnicity, Black/African American participants were generally younger, more likely to have NYHA functional class III–IV, and more likely to have hypertension compared with participants of other races/ethnicities (**Table 3**).
- Asian participants on average had a lower BMI compared with participants of other races/ethnicities (**Table 3**).

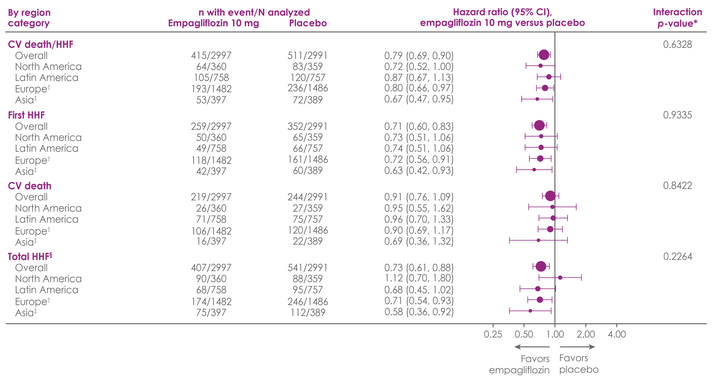
Table 3. Baseline characteristics by race/ethnicity

Characteristics	White (n=4542)	Black/African American (n=258)	Asian (n=824)	Other* (n=362)
Age, years, mean ± SD	72.54±8.92	66.62±11.61	71.16±9.93	69.27±10.71
Female, n (%)	2038 (44.87)	137 (53.10)	302 (36.65)	199 (54.97)
Body mass index, kg/m², mean ± SD	30.68±5.69	30.84±6.28	25.23±4.34	29.08±5.88
Systolic blood pressure, mmHg, mean ± SD	132.00±15.29	134.98±18.66	129.54±15.50	132.85±17.22
NYHA class III–IV, n (%)	882 (19.42)	56 (21.71)	97 (11.77)	65 (17.96)
Duration of heart failure, years, median (IQR)	2.76 (1.02, 5.96)	2.60 (0.97, 5.80)	2.29 (0.81, 5.86)	1.97 (0.82, 4.40)
NT-proBNP, pg/ml, median (IQR)	962.00 (491.00, 1680.00)	792.00 (439.00, 1649.00)	1155.00 (594.50, 2009.50)	863.50 (418.00, 1680.00)
eGFR, ml/min/1.73 m², mean ± SD	59.65±19.22	65.61±26.30	63.93±19.98	61.80±20.38
Medical history, n (%)				
Atrial fibrillation	2460 (54.16)	71 (27.52)	433 (52.55)	92 (25.41)
Hypertension	4174 (91.90)	244 (94.57)	668 (81.07)	336 (92.82)
Diabetes	2208 (48.61)	141 (54.65)	393 (47.69)	195 (53.87)
Treatment for heart failure, n (%)				
All diuretics	3977 (87.56)	238 (92.25)	641 (77.79)	305 (84.25)
Loop diuretics or high ceiling diuretics	3127 (68.85)	182 (70.54)	530 (64.32)	213 (58.84)
ACEi or ARB (excluding ARNi)	3648 (80.32)	214 (82.95)	541 (65.66)	301 (83.15)
ACEi, ARB or ARNi	3734 (82.21)	219 (84.88)	568 (68.93)	310 (85.64)
Beta-blocker	3975 (87.52)	228 (88.37)	650 (78.88)	312 (86.19)
Mineralocorticoid receptor antagonist	1668 (36.72)	97 (37.60)	349 (42.35)	130 (35.91)

*'Other' includes any participant who selected more than 1 race category.
ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNi, angiotensin receptor-neprilysin inhibitor; eGFR, estimated glomerular filtration rate; IQR, interquartile range; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SD, standard deviation.

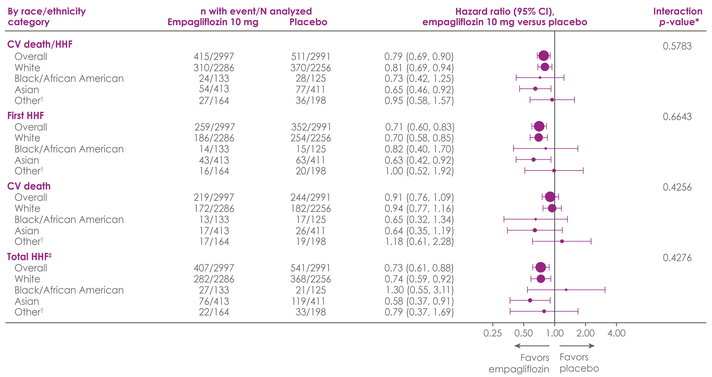
- No interaction between empagliflozin treatment effect on time to first CV death/HHF or its components and region or race/ethnicity was observed (**Figures 1** and **2**).
- Due to the modest sample size of Black/African American participants, the power to identify a potential effect modification is limited.

Figure 1. Treatment effect, empagliflozin versus placebo, for time to first CV death/HHF, first HHF, CV death, and total HHF by region



Cox regression model including terms for age, baseline eGFR, baseline LVEF, diabetes at baseline, sex, treatment, geographic region, and treatment by geographic region.
*Treatment by geographic region.
†South Africa (n=163) and Australia (n=116) are included in the 'Europe' category.
‡India (n=100) is including in the 'Asia' category.
§Joint frailty model including the same covariates as the Cox model.
CI, confidence intervals; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction.

Figure 2. Treatment effect, empagliflozin versus placebo, for time to first CV death/HHF, first HHF, CV death, and total HHF by race/ethnicity



Cox regression model including terms for age, baseline eGFR, baseline LVEF, region, diabetes at baseline, sex, treatment, race/ethnicity, and treatment by race/ethnicity.
*Treatment by race/ethnicity.
†'Other' includes any participant who selected more than 1 race category.
‡Joint frailty model including the same covariates as the Cox model.
CI, confidence intervals; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HHF, hospitalization for heart failure; LVEF, left ventricular ejection fraction.

CONCLUSION

- The beneficial effects of empagliflozin on CV death or HHF events in patients with HFpEF are independent of region and race/ethnicity

Poster 144: 71st Annual American College of Cardiology (ACC) Scientific Session, Washington, DC, April 2–4, 2022.
Presenter: Dr Vijay Chopra, Max Super Speciality Hospital, New Delhi, India; email: chopravk@gmail.com.

Reference
1. Anker S *et al. N Engl J Med* 2021;385:1451–1461.

Disclosures
Vijay Chopra received personal fees from AstraZeneca Pharmaceuticals, Boehringer Ingelheim, and Novartis.

Acknowledgments
The EMPEROR-Preserved trial (ClinicalTrials.gov: NCT03057951) was funded by the Boehringer Ingelheim & Eli Lilly and Company Diabetes Alliance. Graphical support was provided by 7.4 Limited and Elevate Medical Affairs, and supported financially by Boehringer Ingelheim. The author was fully responsible for all content and editorial decisions, was involved at all stages of poster development, and has approved the final version.

SC-US-74093